THE CONCEPT OF "STRESS" IN THE BIOLOGICAL AND SOCIAL SCIENCES[1, 2]

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ABSTRACT–The concept of "stress" was applied to biological and social systems in the first half of this century because it appeared to provide an explanation for the apparently "non-specific" effects of biologic agents, and for the occurrence of illness as a part of the response of people to their social environment. Evidence subsequently accumulated has confirmed that a large proportion of the manifestations of disease are produced by reaction of the host and not directly by the "causal agents" of disease, and that the components of the host's reactions are not in themselves "specific" to any given "causal agent"; it has confirmed that reactions of people to other people, or to the social environment may influence any physiological process or any disease; but it has also indicated that the concept of "stress" does not provide an adequate explanation for these phenomena.

Living organisms are highly ordered and complex biological organizations that maintain themselves precariously over a limited period of time by the interchange of energy and information with the environment. Their reactions to the environment are complex and highly ordered, are based upon information, and are communicative and "logical" in nature. Although the components are "not specific," the reactions themselves may be highly specific to the stimulus that initiates them. These reactions are not random but are "directed" (apparently "purposeful") and tend to preserve the integrity of the organism, and the integrity of its relation to its social group and to its environment. The concept of "stress," which was derived partly from popular usage, and based upon 18th and 19th century mechanical models of "force," "counterforce," and "distortion," does not provide a meaningful scientific description of organism-environment relationships. These are better described by other concepts. The "stress concept" was heuristically valuable in the past, but it is no longer necessary, and it is in some ways hampering at the present.

Few would deny that a significant contribution to the modern understanding of disease was made by Walter Bradford Cannon, Hans Selye, and the late Harold G. Wolff. A feature of modern medicine has been the decline of the concept of the "specific cause of disease" which had grown up in the 19th century largely

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under the influence of Virchow and Pasteur. It is the present disposition to regard diseases as having a variety of "causes," and to look upon every instance of disease as a result of the interaction of a number of factors, each of which could be considered a cause. It is now generally agreed that diseases may be as much a result of the adaptive reactions of the host as they are of the damaging effects of pathogenic agents, and it is widely accepted that the relation of people to the other people around them and to the society in which they live are important causes of disease. The "stress concept" has contributed to this change in point of view. Yet there is a question whether or not the concept itself, which was so fruitful in its time, is any longer adequate or even helpful for our understanding of how the interactions between people and pathogenic agents or between people and society produce disease.

The questions that have been raised about "stress" have to do with whether or not the concept provides an adequate description of the data that are now available to us, and whether or not it is any longer a useful intellectual tool, even when it is used in a descriptive sense. Does the term "stress," as it is used in the biological and social sciences, denote a variable that can be identified unambiguously by objective means, counted and measured, as the term does when it is used in the physical sciences? Is there a "state of stress" in the living organism which can be clearly differentiated from other states? If this is so, does the identification, measurement or description of this state help us to understand how and when various diseases occur? If this is *not* so, are there nevertheless classes of conditions, relationships or events in the social world which can be categorized as "stressful" and distinguished from those which are not?

HISTORICAL BACKGROUND

Origin of the Term

The use of the concept of stress in the social and biological sciences was proposed at a time when a considerable intellectual discontinuity still separated these sciences from a common body of concepts which more or less united the physical sciences. Over the previous four centuries mathematics, physics, chemistry and other "hard sciences" had been woven together gradually into a connected body of knowledge which appeared to describe the non-living "physical world" in a coherent manner. During the 19th and early part of the 20th century it had become possible to describe some fundamental biological processes in terms that were compatible with the current concepts of physics, chemistry, and mathematics; but the "hard sciences" had not yet presented any reasonable body of data or hypotheses which appeared to explain how "thinking," "memory," or "voluntary activity" might take place within a living

organism. Nor were there concepts within these sciences which appeared to explain many clinical observations, such as, for example, the observation that a man might develop more florid diabetes mellitus after he had lost his job, or that he might experience an increased risk of coronary heart disease because his father had only a grammar school education. Faced with the necessity of dealing with such phenomena, the medical and social scientists developed concepts of their own which did not always fit the facts as these were later uncovered. The development of the concept of stress is a case in point.

"Stress" is a term of Latin derivation which was used in the English language to describe human experience and behavior long before it was given a formal scientific definition for use in physics and engineering. "Stress" in the 17th century meant "hardship, straits, adversity or affliction" [1]. During the 18th and 19th century this usage was largely replaced by other uses in which the term denoted "force, pressure, strain or strong effort" exerted upon a material object or a person—or upon a person's "organs or mental powers." It then carried with it the connotation of an object's (or person's) being acted upon by forces from without, resisting the distorting effects of these forces, attempting to maintain its integrity and trying to return to its original state. The word was taken over into science in this sense, and probably the scientific use of the term reinforced the popular usage.

"Stress" in Physics and Engineering

In physics and engineering "stress" became a term that had to do with elasticity. Its use in science grew out of Boyle's investigations of the properties of gases and Hooke's studies of the elasticity of springs in the late 17th century; but the precise definition was not elaborated until the early 19th century by Baron Cauchy [2]. In physics, stress is a concept applied to solid bodies. The term itself is used to denote the internal force generated within such a body by the action of any force which tends to distort the body. "Stress," "strain" and "load" have specific meanings: "stress," measured in dynes per square centimeter, is the ratio of the internal force brought into play when a substance is distorted to the area over which the force acts; "strain" (or "distortion") is the ratio of the change in size or shape to the original size or shape; and "load" is the name often applied to the external force producing the distortion. In general terms the relation between these three is stated as "Hooke's Law": Load = stress = E (Strain). The constant "E" is "Young's Modulus of Elasticity."

It is perhaps worthy of note that the concept of stress as used in physics and engineering turned out to be a highly special concept, applicable in practice only to certain classes of solid bodies, and then over a limited range and under the assumption that these bodies are entirely homogeneous. The mathematics involved in the precise calculations of stress and strain are more complex than the simple linear equation of Hooke's Law would indicate.

"Stress" in Medicine and Biology

Throughout the 19th and the early 20th centuries "stress and strain" (in the non-scientific sense) had also been thought of as causing "ill health" and "mental disease." Thus, in 1910, when Sir William Osler delivered his Lumleian Lectures on "Angina Pectoris" he stated that he found this condition to be especially common among the Jewish members of the business community and he further said that "Living an intense life, absorbed in his work, devoted to his pleasures, passionately devoted to his home, the nervous energy of the Jew is taxed to the uttermost, and his system is subjected to that stress and strain which seems to be a basic factor in so many cases of angina pectoris" [3]. He equated "stress and strain" with "hard work and worry." Furthermore, he said, in a group of twenty physicians "everyone of whom I know personally" the outstanding feature was "the incessant treadmill of the practice of medicine, and in everyone of these men there was an added factor—worry" [3].

About fifteen years after Osler's lecture, Walter Cannon began to use the term "stress" in relation to some of his laboratory experiments on the "fight or flight" reaction. Possibly the use of the concept was suggested to him by the "homeostatic" features of living organisms—their tendency to "bound back," to "resist distortion" and to restore their original state when they are acted upon by an "external force" or disturbing agent of any sort. Cannon appears to have used the term in a *quasi*-scientific sense. Observing evidence of reaction by the adrenal medulla and the sympathetic nervous system when humans or laboratory animals are exposed to a variety of conditions such as cold, lack of oxygen, low blood sugar, loss of blood or "excitement," Cannon stated that his subjects were "under stress" and he more or less implied that the degree of stress might be measured [4].

A decade and a half later, in the late 1930's and in the first half of the 1940's, Hans Selye [5] described in detail the response of laboratory animals to a variety of damaging or "alarming" stimuli such as bacteria, toxins, trauma, heat, and cold, and documented the role of the anterior pituitary and the adrenal cortex in all of these responses. He described a "general adaptation syndrome" and postulated that this syndrome was produced by "non-specific stress." Later he defined the "state of stress" as "the state manifested by a specific syndrome which consists of all of the non-specifically induced changes within a biologic system" [6]. In the body of the article from which this quotation is taken Selye distinguished between the "state of stress" and the "syndrome," and he indicated that the presence of the "state" is manifested only by the appearance of the "syndrome." He stated that the syndrome is a "specific syndrome" and not just any syndrome, and that "it consists of all of the non-specifically induced changes within a biologic system."

The definition of the syndrome by which one recognizes the presence of non-specific stress hangs upon the meaning of the phrase "non-specifically

induced changes." If one takes this phrase to mean "changes induced in the system which are not the result of the direct damaging action of a stressor, but which may occur as a part of the reaction of the system to a variety of stressors," one takes this phrase, I believe, in the way that Selye intended it. The "specific syndrome" by which the stress is manifested consists of "all such non-specific changes," and not just those which occur in any one instance. The syndrome itself is not described in this article, but it is said that "the pattern of the stress reaction (for instance the combination of changes in the pituitary, adrenal, thymus and gastrointestinal tract) is "highly specific." In fact, only the causation of the syndrome is non-specific. From this one can assume that the author had in mind that the syndrome which indicated the presence of stress consisted of that body of phenomena which he described as the "general adaptation syndrome" and its variants.

At about the same time, during the 1940's and early 1950's, Harold G. Wolff and his colleagues, as well as many other physicians, described a variety of diseases as being influenced by "life stress" [7]. Wolff's concept of "life stress" appears to have evolved over the years. In the first edition of his book, *Stress and Disease* [8], he discussed the nature of stress without ever formally defining the term. By implication, from the context in which the term is used, it is apparent that he regarded "stress" as being created by a "man's response to many sorts of noxious agents and threats." It is also evident that he regarded events perceived as threats as capable of creating "stress." He spoke of "bodily changes resulting from "stress" and of "stress-producing factors in the American culture." He also spoke of "changes of form and function with adaptation to stress." In general, it appeared that he regarded "stress" as a state of the human organism.

During the late 1950's when questions had been raised about the nature of the state of stress, Wolff elaborated his thoughts on this point [9]:

> I have used the word [stress] in biology to indicate that state within a living creature which results from the interaction of the organism with noxious stimuli or circumstances, i.e., it is a dynamic state within the organism; it is not a stimulus, assault, load, symbol, burden, or any aspect of environment, internal, external, social or otherwise.

He further stated:

> Noxious stimuli or circumstances may be divided as regards stress into two extreme categories, with myriad intermediate mixed forms resulting in a continuum. A contrast between extremes would be as follows:
>
> Those in the first category may be referred to as unconditional and may be said to act directly, damaging and distorting structure and function. Such stimulation would result from strong mechanical, thermal, electrical and corrosive chemical agents. . . .
>
> Stimuli in the second category may be referred to as conditional and may be said to act indirectly. They may be of themselves biologically inconsequential or of extreme low intensity, and assume significance mainly because of their capacity to act as signals or symbols. They usually have little or no direct noxious effect. The nature of the adaptive reaction they evoke is dependent entirely upon individual past experience and to some degree upon the stock. They are less predictable and less

> stable, readily modified by the setting in which stimulation occurs, and there is commonly no close relationship in time between the stimulus and the response. Behavioral, attitudinal, and other bodily responses are only to a very limited degree appropriate in kind, as well as inappropriate in amount. They may, however, be long sustained and extremely destructive. These complex reactions during stress always involve the central nervous system, and especially the highest integrative functions of the central nervous system. The meaning of the stimuli for the individual makes them assume the nature of "stress" [9].

Harold Wolff's last statement on the subject is contained in the second edition of his book, *Stress and Disease* [10]:

> The resemblance [of the physical concept of stress] to the situation in living systems is remote, yet figuratively the concept is useful, and when employed in reference to human problems merely implies an analogy to the order in non-living systems. Since stress is a dynamic state within an organism in response to a demand for adaptation, and since life itself entails constant adaptation, living creatures are continually in a state of more or less stress.

Selye and Wolff thus agreed that "stress" is a "state" within the organism. Wolff did not say how this state could be recognized, but Selye indicated that its presence could be inferred from the presence of the physiological and pathological changes which it is presumed to produce. Neither indicated precisely what the nature of this state might be, but by implication both made it clear that "stress" in biologic systems is not a "force" in the physical sense, and that it is not measured in dynes per square centimeter, as it is measured in physics. Wolff specifically indicated, and Selye indicated by implication, that the relationship between the magnitude or intensity of the state of "stress" within the organism, and the magnitude or intensity of the external agent or condition which produced this state, is not a linear one, as it is in physics. Without saying so precisely in so many words, both implied that the noxious or damaging agent or the relation of the subject to his society, or whatever else initiated the stress, acted as a stimulus or trigger, and that this trigger induced the organism to elaborate within itself the "state of stress" and most of the subsequent pathological changes. The postulation that the "noxious agent" or circumstance acted as a "signal" or stimulus and (in Wolff's case) the statement that "the conditions which produce 'life stress' always act through the central nervous system" clearly imply that the relation between external "stressor" and internal "state of stress" in a biological system is based upon a communicative or signaling interaction, and not upon the direct and linear interchange of energy which is characterized by the relation of "stress," "strain," and "load" under Hooke's Law.

Parallel Developments in Theoretical Biology

At the time when Cannon, Selye, and Wolff were elaborating their concepts of stress in biological systems, knowledge of the nature of the process of communication and of the importance of "order" and "organization" in

biological systems was developing rapidly. The background for this had been laid in the 19th century. The physicists who developed thermodynamics in that century had recognized the pervasive tendency of the non-living world to become more random, disordered and disorganized. They evolved the concept of "entropy" as a means of identifying and measuring this tendency. The naturalists of the 19th century, by contrast, had been repeatedly impressed with the high degree of order and organization which they found in the living world as they undertook to classify it, and to chart its evolutionary development. The physiologists, following Claude Bernard, had recognized that the life process itself appeared to depend upon the maintenance of relatively constant, rather than randomly changing, conditions within the organism—a point which Bernard emphasized in his description of the constancy of the *milieu internale* [11].

At the beginning of the 20th century, as Walter Cannon described the mechanisms by which the living organism attempts to maintain the constancy of the fluid part of its internal environment, he referred to the general process as "homeostasis" [12]. A fundamental feature of his concept of homeostasis was its recognition that the composition of the internal fluid environment does not actually remain in a steady state, but that it is repeatedly disturbed in one direction or another by the metabolic activities of the animal. The term "homeostasis" actually referred to the continual tendency of the fluid environment to return toward a "steady state" after each disturbance, a phenomenon that Cannon and many others had shown to be based upon a remarkable complex system of buffers and feedback mechanisms which are part of the living organism.

By the mid 1940's Rudolph Schoenheimer [13] had extended Cannon's concept of homeostasis, and had put forward his own concept of the "dynamic steady state," which he had evolved from studies of the molecular turnover within the fat, protein and mineral components of the body. The gist of Schoenheimer's concept was that the constant process of turnover, change, and replacement, which had previously been recognized within the fluid components of the body, goes on within all of the tissues. Every part of the living organism takes part in this metabolic activity. Every part is subject to growth, change, degradation and to the replacement and turnover of its molecular components. The whole living organism, and not just its internal milieu, is in a "dynamic steady state"—a dynamic equilibrium of constantly interacting and inherently unstable biochemical systems. Schoenheimer's view of this fundamental feature of living organisms has been generally accepted since that time.

Almost coincidentally with the publication of Schoenheimer's concept, the physicist Erwin Schrödinger [14] described with great lucidity the differences in order and organization which separate the living from the non-living world. In the non-living world, Schrödinger pointed out, the amount of "free energy"—the energy available for doing work—diminishes steadily, and the amount of disorder and disorganization increases steadily. This is, in effect, the Second Law of

Thermodynamics. In the living world, on the other hand, over the course of biological evolution, the total amount of order and organization has increased steadily. Furthermore, over the lifetime of any one living organism, that organism not only maintains its own organization in the face of many influences that tend to disorganize it, but even increases the degree and complexity of its organization during parts of its life cycle. The living world thus appears to violate the Second Law of Thermodynamics–but, as Schrödinger also pointed out, this violation is only apparent, and not real; for living organisms maintain their level of organization only during the period of their lifetime, and they do this at the expense of consuming free energy, and (in the case of animals and some plants) consuming other highly organized substances. Over the long run, they do not violate the Second Law of Thermodynamics.

In technical terms, those who have accepted Schrödinger's general thesis–and this now includes most theoretical biologists–say that living organisms "maintain their dynamic steady state by the acquisition of free energy and 'information' from the 'environment'." The term "information" is used in this context to denote "matter or energy in a pre-existing state of organization," whether this organization is in the form of chemical elements arranged as edible proteins, or in the form of lights and shadows, sound waves or patterns of pressure that create visual, auditory or tactile "messages."

This use of the term "information" came about because developments during the first half of the twentieth century had indicated that the transmission of messages and the carrying out of logical processes are like the living process in that they are dependent upon the presence of "order," lack of ambiguity, uniqueness and a state of matter or energy that is the opposite of randomness. The "information content" of any system was found to be measurable by its degree of order. "Information" was recognized by the physicists of the 1920's as being essentially the opposite of "entropy." The mathematical properties of "information" were described later in the 1940's by C. F. Shannon [15] as "information theory," which is, in a certain sense, a special case of the theory of thermodynamics. Practical applications of the understanding of the basis for communication led to the rapid development of communication systems, and to the development of logical, computing, and calculating machines in the 1930's and in subsequent decades. It also led to an understanding of the basis upon which the sense organs and the nervous system of animals operate, and to the comprehension of the probable logical basis for the neural phenomena involved in "perceiving," "remembering," "thinking," and "voluntary activity."

These developments, occurring in the period during and immediately after the time when Cannon, Selye, Wolff and others were evolving their concepts of "stress" in biological systems, have produced a body of knowledge which has made it desirable to reconsider this theory, and perhaps to amend it, or to discard it.

SOME PRESENT CONCEPTS OF THE NATURE OF MEN AND OF THEIR RELATION TO THEIR SOCIAL ENVIRONMENT

"Man" and "Environment"

This paper has been written from the biological point of view that is shared by the natural sciences. At the present time, this point of view does not appear to be in fundamental conflict with that of the social and behavioral sciences. The concept of "man" that is presented here is based upon the biological concept that the higher forms of life exist as discrete and more or less independent organisms, and that each organism is surrounded by an "environment." The maintenance of the life of the organism is regarded as being dependent upon a constant interaction between the organism and its environment. In technical terms, the living organism is regarded as a finite, highly organized hierarchy of biological systems which maintain themselves in a "dynamic steady state" over a limited period of time by the consumption of free energy, and by the continual interchange of matter, energy and information with the "environment." The "dynamic steady state" is a dynamic equilibrium of constantly interacting and inherently unstable biochemical systems.

"Free energy," broadly speaking, is defined as "energy" that is available for doing work.

"Information," broadly speaking, is defined as the property of matter and energy that has to do with its degree of order, or lack of randomness [16]. It is the property which provides the basis for organized systems and structures, for "non-random" and apparently "purposeful" behavior, and for communication.

The "environment" of an organism, in the broadest sense, is defined as all of the world that is outside of its boundaries; more specifically, the "environment" is considered to be made up of those parts of the universal system with which the organism interacts.

The boundaries of a man—the limits at which his environment begins—are considered to be his skin, the lining epithelium of his respiratory tract, the lining epithelium of his gastrointestinal tract, and the lining epithelium of his kidneys and urinary tract. These and his "organs of special sense" are the primary interfaces between him and his environment. The "organs of special sense" are the eyes, the ears, the olfactory organs, the taste organs, and the special organs within the skin and inside the body which provide for the senses of touch, pain, temperature, pressure, position in space, and acceleration. It is of passing interest to make note of the fact that, by this biological definition, the clothing on a person's back, the air in his lungs, the food in his gastrointestinal tract and the urine in his bladder are all parts of his environment, since they are, strictly speaking, outside of the boundaries of the human organism.

Interrelations Between Man and Environment

The maintenance of human life is considered to be dependent upon a constant interchange of water and heat across the skin; of water, carbon dioxide and oxygen across the epithelium of the lungs; of food, minerals and water across the epithelium of the gastrointestinal tract; of water, salts and organic substances across the epithelium of the kidneys; and of information across all of these interfaces, and especially across the organs of special sense.

All of these interchanges with the environment are associated with an interchange of information, as well as with an interchange of energy. For example, most foods are highly organized organic material with a considerable "information content." Since they are only partly broken down before being absorbed, the eating of food, as Schrödinger pointed out, in itself represents a considerable acquisition of the "information" (order), as well as an acquisition of energy from the environment. However, the interface between a man and his environment that is primarily concerned with the acquisition of information, as such, from the environment is represented by the organs of special sense. These organs are closely coupled with the central nervous system and, through this, to the neuroendocrine effector systems. This arrangement makes it possible for the human organism to use the information that is acquired by the sense organs in order to draw inferences about those aspects of the environment which do not impinge upon it directly, but are distant from it in time and place; and this arrangement also makes it possible for the organism to organize adaptive responses to the environment which involve the entire human system.

The gross interchanges of energy between a man and his environment amount to approximately 2,500 to 4,000 kilogram calories per day. Most of this energy is absorbed by the man as "food." Part of it is used for muscular activity, but part of it represents that "consumption of free energy" which is required to maintain the metabolic processes that are essential to life.

By far the largest number and variety of the interactions between men and their environment are based not upon interchanges of energy, as such, but upon interchanges of information. A significant part of these informational interchanges is associated with the digestion of food, with immune responses to chemical and microbial agents, with the elaboration of defense mechanisms against such agents, and with other activities which we do not ordinarily think of as having a large content of communication, but the largest proportion of the informational interchanges between men and their environment are carried through the mediation of the sense organs and the central nervous system. A very large part of them are associated with efforts to adapt to aspects of the environment which do not impinge upon a man directly, but are at a distance from him in time and place, and a very important part of this "environment at a distance" is made up of other people and the social group of which a man is a member.

Potential Physiological Effects of Communicative Interactions with the Environment

At the present time, it is generally agreed that responses to information acquired by the sense organs, and processed by the central nervous system, can lead to profound changes in the vital processes of men. A considerable body of detailed evidence relating to this point has been accumulated since the "stress theory" was first elaborated in the 1940's. It is recognized that the effectiveness of the nervous system as an organ of adaptation is dependent upon its capacity to influence the activity of the organism, as a whole, and to integrate the functions of its various organ systems into complex patterns of organismic behavior.

The ability of the central nervous system to control those modes of behavior that are mediated by the skeletal muscles—the "voluntary behavior"—has been understood since the nineteenth century. Its ability to influence organ functions which are regulated by the autonomic nervous system has been clear since the days of Cannon. Knowledge of its ability to regulate the activities of the glands of internal secretion, and through these, to influence a wide variety of intracellular processes, including all phases of metabolism, growth, and reproduction, has accumulated steadily since World War II [17]. It is now generally agreed that there is no cellular mechanism or general metabolic process that cannot, in some measure, be influenced by neuroendocrine mechanisms.

In other words, it might be said that, in man and in the higher animals, reactions to the environment which are mediated by the sense organs and the central nervous system have the capacity to influence any process within the organism that can be influenced by the gross motor behavior of the organism itself, or by the alteration of any function of either the organism or of its component parts, which can be influenced by the skeletal or autonomic nervous system, or by the glands of internal secretion, acting alone or together.

The effects upon physiological processes that can be produced simply by the gross "voluntary" motor behavior of a person are worthy of note. They include not only the effects created by the total amount and type of muscular activity that he undertakes, but also the effects of the amount and types of food and fluid that he ingests, and the effects of such "voluntary" activities as the ingestion of medication, alcohol and drugs, and the smoking of tobacco.

In addition to these, the effects that can be created by the "autonomic" or "involuntary" segment of the nervous system may have important short or long term influences upon the function of any muscular or glandular organ which is innervated by this system. By this means, there may be produced effects upon such physiologic processes as sweat and sebum secretion; upon the secretion of the aqueous humor into the eye; upon nasal and bronchial secretion and motor activity; upon salivation; upon the motor and secretory activities of the esophagus, stomach, biliary tract, pancreas, and large and small intestines; upon

the engorgement, erection and secretion of the genital tract; and upon blood pressure, heart rate and the tonus of the peripheral vessels.

Beyond these, the endocrine system, acting either directly or through a variety of complex interactions with the nervous systems, may have a pervasive influence upon enzyme systems, metabolic pathways and membrane permeabilities at molecular and intracellular levels. These in turn may have important effects upon such diverse processes as cell division, growth, maturation, energy metabolism, fluid and electrolyte metabolism, inflammation, antibody formation, ovulation and spermatogenesis.

Thus the potential magnitude of the effects upon the physiologic processes of men that may be created by neural regulatory mechanisms appears to be as great as the effects which can be produced by any other influences upon these processes, not even excluding those which destroy or permanently damage the systems that are involved in them. As a part of their reaction to their social environment, humans can damage themselves to the point of death by their "voluntary activities" in sports, in hazardous recreations, in hazardous occupations, or by suicide. By their voluntary sumptuary habits they can create gross obesity of any magnitude, or malnutrition to the point of starvation, and all of the adverse effects of the various addictions and intoxications which arise from the use of drugs and chemicals. During the course of their adaptations to their social environment, direct neural regulatory effects upon their organs can produce such pronounced phenomena as total nasal obstruction and profuse secretion on the one hand, or a dry nose and almost complete absence of secretion on the other hand; variations in lower bowel function, ranging from complete constipation to continuous hypermotile diarrhea; variations in the heart rate, ranging from a transient sinus arrest to a sinus tachycardia greater than 180 per minute; and changes in blood pressure, ranging from transient hypotension without detectable blood pressure, to systolic pressures greater than 200 millimeters of mercury. In the same manner, combined neural and endocrine regulatory mechanisms can produce phenomena such as rapid changes in circulating free fatty acids and in ketonemia; the release of liver glycogen with hyperglycemia; suppression of ovulation; and changes in renal water transport, varying from a diuresis of greater than 10 centimeters per minute to a total suppression of urine formation.

Data from clinical observations suggest that motor and secretory effects upon the respiratory and gastrointestinal tracts, tachycardia, suppression of menstruation and ovulation, and similar phenomena, when neurally induced as a part of reactions to the social environment, may last for months or years. It seems probable that neuroendocrine effects upon the rate of progression of neoplasms, the severity of diabetes mellitus, or the course of autoimmune disease, or inflammatory processes, also may persist for months or years. There is information suggesting that somatic growth and maturation may be seriously

influenced by such processes. The available evidence thus suggests that the physiological effects of neuroregulatory mechanisms evoked in response to social stimuli in man may be as prolonged as they are pronounced.

It also appears that the frequency and intensity with which neuroendocrine reaction patterns are elicited in response to environmental stimuli can be specifically altered by the experience of the organism. Voluntary patterns of motor activity can of course be "learned," and it is generally agreed, in fact, that most of those exhibited by adult humans are. The available evidence also suggests that all of the "involuntary" neuroendocrine reaction patterns can be "learned" also. It has been known for many years that muscular and glandular reaction patterns, which are influenced directly by the autonomic nervous system (e.g., the pupillary reflex or the cardio-accelerator reflex) can be "conditioned" by Pavlovian or "avoidance" conditioning. More recently, it has been shown that neuroendocrine mechanisms, such as the posterior pituitary mechanism which controls antidiuretic hormone secretion, can be made the subject of Pavlovian conditioning also, and that by this means both water diuresis and water retention can be "learned" in response to environmental stimuli [18]. Even more recently, Miller and his associates [19] have demonstrated that "operant" or "reward" conditioning can be used to produce a wide variety of learned responses in physiological processes which are regulated by autonomic and by neuroendocrine mechanisms.

All of these observations have provided a reason for believing that the changes in bodily function which may occur under the influence of the central nervous system, and which may be elicited in response to social stimuli, not only may be profound and prolonged, but also that they may be elicited by stimuli to which they were not originally relevant. These characteristics of neural adaptive mechanisms are consistent with what we know about cellular adaptive mechanisms.

The "Adequate Stimulus"

An important question, both now and in the past, has been the question of what might be an "adequate stimulus" to the human nervous system to cause it to evoke changes in organ function of such magnitude and duration. The fact that the nervous system is fundamentally a system for processing information determines the answer to this question. It responds in a highly specific ("non-random") manner to the patterns of information which it receives. Some of its responses are "wired into the circuitry" in the sense that they seem to be genetically determined by the structure of the system. Other response patterns, such as the motor patterns involved in walking or those that are involved in certain forms of speech, are apparently both "learned" and "innate" [20]. They are apparently "programmed" as a result of the experiences of the individual

organism, which lead it to put together in an orderly fashion presumably innate patterns of muscular activity which were not previously organized in this manner. Many "learned" reaction patterns are thought to be of this nature. They appear to involve the orderly arrangement of innate behavior patterns into more complex patterns of "learned behavior."

The same appears to be true of the "evaluation patterns" of the central nervous system. Some "alarming" stimuli, such as loud noises, for example, are apparently innately "wired in" to produce an alarming or arousing reaction in man, and in almost all of the higher animals. However, a name or a written word becomes "alarming" only through a process of learning. By and large it appears that the stimulus which is adequate to produce a profound or sustained behavioral or physiological response is "non-specific" only in rather general terms, insofar as it is based upon innate patterns that are in some way tied to alarm, aggression, depletion or sexual arousal. However, for the most part, the "adequate stimulus" is likely to be one that has acquired an added significance which has been learned from the past experience of the individual, and the significance of the stimulus may be highly specific to that individual alone.

The stimuli that arise in the social environment and lead to significant physiological or behavioral responses in people are likely to be those that signify changes in important relationships within the social group.

The study of animal behavior and of animal social groups has made us aware of the fact that the social group is a biological phenomenon of pervading importance, and that social groups are fundamental biological adaptive mechanisms. All of the higher animals are social animals. From birth to death they exist as members of organized groups made up of other members of the same species. Within its social group each animal has a highly specifiable set of relationships to the other animals. These change in an orderly manner with its age, and with its activities. They are closely analogous to the role relationships in human social groups. The animal in a social group behaves in a manner such as to maintain its role relationships, even at the expense of its health and life.

For most of the higher animals, as well as for man, other members of the same species are among the critical elements of the environment [21]. Within animal social groups, as within human social groups, the complex hierarchical relationships that are accompanied by complex and circumscribed forms of role behavior cover a wide variety of activities, but they are especially centered about food gathering, defense, courtship, sexual relationships, and the care of the young. Because role relationships are such an important part of their lives, the higher animals respond vigorously to the presence in the environment of other members of the same species. Any information that implies to an animal that the appearance of another animal might lead to a change in its role relationship within the social groups is highly meaningful to the animal that receives it, and is liable to be associated with pronounced behavioral or physiological changes.

Neither animal nor human social groups behave as if the biological needs of

their individual members take precedence over other considerations. They behave, rather, as if the needs of the group take precedence over the needs of the individual. They behave as if the primary duty of the individual is to fulfill the various social roles in which he finds himself. Social groups appear to make provisions for ameliorating the demands of social roles only when these are grossly destructive to the individual. Under certain circumstances a human social group may even demand that some of its members participate in potentially fatal activities, as nations do, for example, when they draft men for military service.

The requirements of social roles, and of interpersonal relations, are among the most frequent sources of major biological challenges that are encountered by men in modern societies. For most people in modern societies there is usually no problem obtaining enough food, fluid, clothing and housing to maintain the integrity of their bodily composition, the likelihood of an attack by a major predator, other than a human, is vanishingly small, and potential sexual partners are plentiful, even though their availability may be limited by the rules of the social group. In modern societies, the exposure of men to pathogenic bacteria, viruses, and other microbial predators has been reduced, and the defense mechanisms of the individual have been reinforced by various means. Although the exposure of men to noise, electromagnetic radiation, and micro-chemical pollutants in the environment may have increased, the amount of overt human disease which can be attributed to these factors has not yet increased in proportion, as the amount of disease which was formerly caused by other factors, such as bacterial infections and malnutrition, has been reduced. On the other hand, life in human societies continues to be associated with an abundance of biological challenges that arise out of social and interpersonal relations.

It is quite possible that the frequency and duration of these challenges may have increased with the increasing complexity of society. Very few men in any modern society can devote themselves primarily to the satisfaction of their own homeostatic needs. Complex social relationships require that people be at certain places at certain times, that they perform certain tasks with a certain speed and accuracy over sustained periods of time, and that they maintain certain relationships with other people, and perform certain services for them. These role requirements, in general, take precedence over fatigue, boredom, sleeplessness, and moderate degrees of discomfort. Members of human societies cannot give free expression to either their aggressive or their sexual drives as they see fit. In addition, the network of communications in modern societies provides people with information about many more potential threats and challenges than they can cope with by any immediate action. Thus there is every reason to believe that life in such societies provides many opportunities for important biological challenges to arise out of the relation of men to the social group, or to the other people in it. It is quite conceivable that these may produce direct neuroendocrine responses, as well as overt behavioral responses, which might have major physiological consequences.

"STRESS THEORY" IN THE LIGHT OF MODERN KNOWLEDGE

"Stress" as a Mediator of Physiological Changes

In the 1940's the concepts of "stress" and of "life stress" were applied to biological and social systems because they appeared to provide an explanation for the apparently "non-specific" effects of biologic agents, and for the occurrence of certain pathological phenomena, and of certain illnesses, as a part of the response of people to their social environment. At the present time, the "stress" explanation is no longer necessary. It is evident that any disease process, and in fact any process within the living organism, might be influenced by the reaction of the individual to his social environment or to other people.

It is clear that there are a variety of physiological mechanisms by which this might occur. These mechanisms might involve not simply the anterior pituitary and the adrenal cortex, but any combination of neural or hormonal effector systems of the organism. The activities of these effector systems might be initiated directly by the activity of other effector or connector systems, or indirectly by changes in the internal environment of the organism. They are often coordinated by the central nervous system. These mechanisms are either understood or potentially understandable on a straightforward physiological basis. It is not necessary to invoke a special variable called "stress" in order to understand their occurrence; in fact, it seems illogical to do so. It is hard to think of a single general state of the living organism which could evoke such a wide variety of internal reaction patterns that are so closely attuned to coping with the internal and external disturbances which initiate them.

Other difficulties about the concept of stress are apparent. It is hard to conceive of a "state of stress" within an organism which is qualitatively different from any other state of being alive. Life is precariously dependent upon constant metabolic activity. Every part of the organism is involved in this activity. It is subject to a continual process of growth, change, degradation and replacement, while only the configuration of the whole—the "dynamic steady state"—survives and abides. This configuration is constantly threatened with disorganization. Every metabolic activity within the organism and every transaction between the organism and its environment, every ion transfer, concentration change, secretion, contraction, ingestion or excretion disturbs the dynamic steady state, is a threat to the integrity of the organism, and requires some adaptive reaction if the steady state is to be restored. The ordinary activities of daily life—the ingestion of food, or the failure to ingest food; muscular activity, or the absence of muscular activity; breathing, or not breathing; sleeping, or not sleeping—all affect the dynamic steady state. Their effects are not qualitatively different from those of the "stressors" that are used in the laboratory. It has been said aptly that "to be alive is to be under stress."

The "non-specificity" of the state of stress also creates problems. It is true that the effector systems of the living organism are limited in number, even

though their number is very large. It is also true that there are certain response patterns of the organism, such as inflammation, for example, which are evoked under a wide variety of circumstances and found in a large number of diseases. It is also true that reaction patterns involving the interior pituitary and the adrenal cortex are involved in the response to a very large number of biological challenges. The unique and essential characteristic, however, of the response of the living organism to its environment is not its lack of specificity, but its high degree of specificity. The organism survives because its response to a challenge to its integrity is directed specifically at the biological threat that is represented by the challenge. It is true, for example, that the response of the human organism to mechanical damage, to thermal damage, to bacterial invasion, and to ruptures of interpersonal relations, may all have elements in common; but a fracture of an ankle, a burn of the skin, pneumonia in the lung, and a reaction of suppressed rage and grief, are very different reactions. An animal which responded to a bacterial invasion of its lung by creating inflammation and new bone in its left ankle would not survive very long. A fundamental feature of life is the capacity of living creatures to develop non-random reactions which are specifically directed at counteracting the effect of threats to their integrity.

One must take cognizance of Wolff's contention that disorders associated with "life stress" are likely to be "inappropriate in kind as well as in amount," for this would mean that they are, to a certain extent, "non-specific." Even though Wolff and some of his colleagues, as well as many of the psychoanalytically-oriented investigators of the 1940's and 1950's, did maintain that the "organic component" of "psychosomatic reactions" had a "symbolic" (in Wolff's terms), or "unconscious" (in psychoanalytic terms), and "highly specific" psychological meaning for the subject, Wolff might have said that they were, nevertheless, "biologically inappropriate." He might have said, for example, that the response of the organism to a bacterial invasion of the lung may be represented by the consolidation of a part of the lung. This consolidation he would regard as a defense mechanism, effective in dealing with bacterial invasion, and therefore appropriate in kind, even though it might in some instances be inappropriate in amount and thus, in itself, somewhat damaging to the organism. On the other hand, he would say that when a man has a disagreement with his wife, which threatens to damage the relation between them, and when at the same time he suppresses the anger and the dependent feelings which develop in him as a result of this disagreement, and when he also develops an active peptic ulcer, the peptic ulcer represents a reaction to the life situation which is inappropriate in kind as well as in amount. By implication, the more appropriate reaction would be a direct expression of the aggressive, hostile, and dependent feelings which the life situation has aroused in the man.

Two comments are pertinent to the points that Wolff might have raised. First, since men are social animals, and since the maintenance of social relationships has a biological importance for men that overrides the importance of maintaining their own physical health, it is not at all clear that the reaction of

suppressing rage and avoiding a threat to dependency is, in itself, "biologically inappropriate" for a man who has a disagreement with his wife, even though it activates his ulcer. Under most circumstances it is quite likely that the biological response of suppressing one's rage and attempting to mollify one's marriage partner is more appropriate than the free and uninhibited expression of these feelings, which might further damage the marriage relationship. The "appropriateness" or "inappropriateness" of this reaction is at least a matter of judgment. Secondly, the adaptive mechanisms of living organisms, effective and finely tuned as they may be, are nevertheless imperfect and to some extent misdirected in many cases. This appears to be related, in part, to the fact that the evolution of adaptive reactions has not proceeded as rapidly as the changes in the situations which evoke these reactions, and there are many vestigial components of these reactions which are not directly useful and may be damaging. If the man had decided to express his rage rather than to suppress it, the raised voice, the suffused face, the elevated blood pressure, and the erect hair on the back of the neck which might accompany his expression of rage would be as "biologically inappropriate" as the development of gastric hypermotility and hypersecretion which presumably accompanied the suppression of the rage. Imperfection and the capacity for becoming misdirected are not simply characteristics of human adaptations to social situations. The allergic and hypersensitive states, and particularly the "autoimmune reactions" that can occur in response to antigenic agents, are examples of other defense mechanisms which can be termed "inappropriate" in kind as well as in amount, and which can produce crippling disease.

A practical difficulty with the use of the concept of stress in relation to social and biological systems has been the apparent analogy to its use in physics and engineering. This has led to many and futile efforts to "quantify" and to "measure" stress. Some of these efforts have been based upon the rather uncritical assumption that there is a linear relation between events outside of the organism and events within the organism. At the time when the concept was being evolved, there was an imperfect understanding of the role of communication in biology, and it was not clear that many of the relations between organisms and environment are fundamentally of a communicative nature. Harold Wolff's later statement that "life stress" acts through the nervous system, and his description of a nonlinear relation between the stressful events or situations outside of the organism, and the occurrence of a state of stress within the organism, made it evident that he had become aware of the communicative nature of this relationship. Yet, his continued use of terms such as "stress," "strain," and "load" suggest that he had not entirely freed himself from the simpler analogies that were appropriate to the effects of force upon solid bodies. The inability of all of the authors of stress theories to define the "state of stress" in a manner that can be quantified has discouraged attempts to

"measure stress" within the living organism; but there are continuing efforts to quantify the degree of stressfulness of events or situations in the social environment.

It might be said that the observations of those who advocated the stress concept in the 1940's and early 1950's not only have been supported by subsequent knowledge, but have been vastly extended; but the invocation of a "state of stress" as an explanation for the pathogenesis of these phenomena has not been proven correct, and it has been necessary to modify this explanation in the light of later knowledge.

The Concept of "Stressful" Events or Situations

If we grant that the concept of a "state of stress" of living organisms is inaccurate and unnecessary for explaining the phenomena of disease, is it not possible, nevertheless, that there are classes of conditions, events, or relationships within the social environment, which in themselves are inherently "stressful," "noxious," or "disease-producing"? Does not "life stress" still exist in the colloquial sense of "hardships," "straits," and "difficulties" in which it has long been used? Do not the observations of Holmes and others [22, 23] that significant life changes can be rank-ordered in a consistent manner, indicate that the concept of "stressful" situations does have validity? If the death of a marriage partner is many times more likely to initiate disease than the receipt of a summons for parking, can we not assume that the first event is inherently more stressful?

The answer to this is probably "no." Efforts to equate exposure to "hardships," "straits," and "difficulties" with the appearance of disease have produced ambiguous and sometimes confusing results.

As long ago as World War II, it was observed that military units in base camps or in rear areas might have a higher level of sickness and disability among their men than they experienced in forward areas where the threat of military action was more imminent [24]. It was found that some people who were removed from their homes and their middle-class patterns of life and thrust into concentration camps lost their asthma, peptic ulcers, migraine, ulcerative colitis and other evidences of illnesses then thought of as "stress diseases," but became ill and died of infectious diseases, malnutrition and trauma [25]. During the war the severity of diabetes mellitus diminished in many areas which were then under military occupation even though other illnesses such as hyperthyroidism were said to have become more frequent [26, 27]. There have been similar reports since that time.

In the day-to-day observation of clinical disease it has appeared that many illnesses become more severe in the setting of difficult life situations, but that some, such as migraine [28] and multiple sclerosis, are likely to be more severe

in some people, not during a period of difficulty, but after the difficulties have ended and the demands upon the individual have been, to some extent, relieved. Certain other illnesses, such as the common cold and vasomotor rhinitis, sometimes appear in a setting of pleasurable excitement [29].

Major "life changes" are not necessarily associated with disease. During World War II the expected epidemics of disease did not appear in the population of London during the rigors of the "Blitz" in the 1940's, nor did they appear among those who had been evacuated to safer areas [30]. When we studied some of the refugees from the Hungarian Revolution who had been abruptly uprooted from their country in 1956 and brought to the United States within a period of a few months, we found that in this setting evidence of serious illness or of the exacerbation of pre-existing conditions was minimal [31].

On a broader scale it may be pointed out that populations in pre-industrial and underdeveloped societies may experience a high level of morbidity and mortality from malnutrition, infections, infestations, trauma and failures of human growth and development, and that a rise in the standard of living of the members of such a population, accompanied by an increase in the level of nutrition, protection, comfort and education, may be associated with a major decline in the frequency of diseases of this sort; but this decline may be accompanied by the appearance of many other diseases such as obesity, hypertension, atherosclerosis, diabetes mellitus, and cancer.

The data from whatever source suggest that one cannot simply equate "hardships," "straits," and "difficulties" with a state of health. It appears, rather, that patterns of illness and the frequency of certain kinds of illness change with changing circumstances.

In view of the fact that people react to their "life situations" or social conditions in terms of the meaning of these situations to them, it is difficult to accept the hypothesis that certain kinds of situations or relationships are inherently stressful and certain others are not. The likelihood is that the consistencies that appear in the findings of Holmes and others are based upon certain consistencies in the social relationships of many people in many societies. Most of the people that have been examined by those who studied "life changes" have lived in societies that base the mature human sexual relationship upon a continuing association between one man and one woman, which is more often than not sanctioned by some form of recognition by the social group. The disruption of such an important social relationship might be expected to have important consequences for the individuals involved. However, because people do react to the meaning of their life situation *to them*, one would not expect that this would be a universal finding; indeed, one can readily think of circumstances under which the loss of a marriage partner would be a relatively trivial or neutral event to an individual, whereas the receipt of a summons for parking could have disastrous implications. One can accept that events and situations can be grouped into those that are more likely to be meaningful and

those that are less likely to be meaningful, especially if one is dealing with people from the same level of the same society; but it is difficult to assume that one sort of event is intrinsically more "stressful" than another.

A SUGGESTED ALTERNATIVE

One who undertakes to criticize a theory such as the theory of stress and to indicate that it may be inadequate today is fortunately not required to put forward a new theory to replace it. Possibly no new theory is needed. The accumulation of data and the understanding of mechanisms have proceeded so steadily during the past three decades that observations and data may now be able to stand where theory was necessary in the past. The present state of knowledge, as I understand it, suggests that if one wishes to study the relation between a social variable and a health variable, one should begin with the hypothesis that both kinds of variables are often loosely and variously defined; that the links between them, if any, may be of a number of kinds; and that the results of any investigation may be dependent upon the definitions and methods of measurement that are used, and the population that is studied.

It follows that one should first make as precise, as complete, and as concrete a definition and measurement of the social variable as one can. One should specify in detail the population or the individuals that are being studied and the time and the circumstances of the study. One should try to identify as completely as possible those characteristics of the individuals involved which appear to be relevant to their reaction to the social variable, and which also appear to be relevant to the health variable that is being studied. This health variable also should be identified, enumerated, and measured as accurately as possible. When relationships are observed, it should not be assumed that these are general relationships until other studies of other populations, using other methods of measurement, provide evidence of the extent to which the findings can be generalized.

That the relation of people to their society and to the people around them can influence the incidence, the prevalence, the course, and the mortality of diseases seems clear enough. The questions at issue are the questions of when they do so, under what circumstances, by what mechanisms, and to what extent. Precise answers to these questions will not be forthcoming without a great deal of scientific effort.

A question likely to remain moot is the question of whether or not a social condition or an interpersonal relationship can ever be a "sole and sufficient cause" of disease. The complexity of this question is such that a clear-cut answer undoubtedly will not be forthcoming at any early date. However, the bulk of experience to date suggests that this answer, when it is finally forthcoming, will be "no." At a time when it is considered that the presence of micro-organisms is not a sole and sufficient explanation for the occurrence of infectious disease,

that the presence of abnormal genes is not a sole and sufficient explanation for the occurrence of genetic disease, that the experience of trauma is not a sole and sufficient explanation for the occurrence of traumatic disease, and that the availability of alcohol and narcotics is not a sole and sufficient explanation for the occurrence of alcoholism or drug addiction, it is unreasonable to suppose that exposure to a certain kind of interpersonal relationship or social condition will be found to be a sole and sufficient explanation for the occurrence of disease of any sort. The likelihood is that social phenomena will interrelate with other apparent "causes." One will indeed see hard working, striving, impatient men who drop dead suddenly at the end of a hard day's work. If one performs population studies on a prospective basis, one is likely to find that this occurs most frequently among middle-aged and elderly men who are hyperlipidemic, who have elevated blood pressures, who have a long history of smoking cigarettes, and who have evidence of disorders of their cardiac conduction systems; and it will be very rare, indeed, that such a sudden death will be found in a healthy young woman who has none of these conditions.

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